REMARKS

Claims 4-6 and 8-24 remain pending in the case. Claim 24 is the sole claim under examination on the merits, claims 4-6 and 8-23 having been withdrawn by the Examiner as drawn to a non-elected invention. No new amendments are requested at this time.

Claim 24 says:

24. A composition comprising, as an active ingredient, a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1.

SEQ ID NO:1 is a 17-nucleotide RNA sequence that corresponds to positions 1723-1739 of Wnt1 mRNA, *i.e.*, at the 3' end of the Wnt1 mRNA coding sequence, including two of the three nucleotides of the stop codon. See page 6, lines 4-11, of the substitute specification filed September 28, 2006. Claim 24 was rejected as unpatentable under 35 USC § 103(a), on two alternate grounds. Each ground is discussed in turn below.

1. Claim 24 was rejected as obvious over Sugiyama et al. (US 6,225,051 B1) in view of Ast et al. (Nucleic Acids Res., 1997, 25:3508-3513); Mallardo et al. (Mol. Biol. Cell, 2001, 12:3875-3891); Jin et al. (Cancer Res, 2003, 63:6154-6157); and Vickers et al. (J. Biol. Chem., 2003, 278:7108-7118). The Final Office action at pages 3-4 points to Sugiyama et al.'s disclosure of what Sugiyama et al. labels "SEQ ID NO:12." Sugiyama et al.'s SEQ ID NO:12 is a 21-mer DNA sequence of which nucleotides 2-18 are complementary to the 17-mer SEQ ID NO:1 of the present application. Sugiyama et al. utilized this 21-mer DNA as a RT-PCR primer (see Example 3 and Table 3). The Office action acknowledges that "Sugiyama et al. does not teach a single-stranded RNA or double-stranded RNA comprising RNA of SEQ ID NO:12."

To make up for this shortcoming, the Office cites Ast et al., Mallardo et al., Jin et al., and Vickers et al. for their teachings about how to make and use RNA-based antisense and siRNA compounds in general. According to the Final Office action at pages 4-5,

> It would have [been] obvious to one of ordinary skill in the art at the time the invention was made to synthesize an RNA antisense nucleotide molecule of SEQ ID NO:12 of Sugiyama et al.
>
> One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to use the RNA-based antisense nucleic acid to detect the RNA level of WT1 in [a] cancer cell sample or inhibit the WT1 expression level at the RNA level, because SEQ ID NO:12 of Sugiyama et al. that is fully complementary to the entire 17-mer SEQ ID NO:1 was known to hybridize specifically with the WT1 nucleotide sequence, and because making and using RNA-based antisense oligonucleotide compounds (including siRNAs) were within the technical grasp of one of ordinary skill in the art at the time the invention was made.

Applicants traverse.

First, Applicants note that the claim recites that the composition contains "a single stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1." An RNA "that is perfectly complementary" to a reference sequence must contain exactly the same number of nucleotides as the reference sequence—otherwise it would not be its perfect complement. Applicants make this point because it appears that the Office has interpreted the term "that is perfectly complementary" to encompass a nucleic acid, such as Sugiyama et al.'s SEQ ID NO:12 primer, that is longer than the reference sequence and so includes sequence on one or both ends that is not complementary to the reference sequence. (Sugiyama et al.'s SEQ ID NO:12 contains four nucleotides more than permitted by claim 24: three extra nucleotides at one end and one at the other.)

It is possible that the Office has arrived at this broad interpretation of claim 24 by reading the "comprising" term in claim 24 to mean that the claimed RNA can broadly include sequence *in addition to* the 17 nt sequence that is "perfectly complementary" to SEQ ID NO:1. See the Office action's generic discussion of the term "comprising" at page 3. If this is indeed how the Office is reading the term "comprising" in claim 24, Applicants point out that "comprising" in

claim 24 applies to the description of the composition ("A composition comprising..."), and not to the description of the RNA that is one part of the composition. Thus, while the overall composition can contain unspecified ingredients in addition to the specified RNA, the specified RNA itself is precisely limited to "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1."

As there is no disclosure anywhere in the cited art of any 17-mer nucleic acid that meets the "perfectly complementary" limitation of claim 24, and there would have been no reason apparent to one of ordinary skill in the art to shorten the 21-mer primer DNA disclosed by Sugiyama et al. in such a way so that it meets that limitation, a *prima facie* case of obviousness has not been made out for at least that reason.

Second, even if Sugiyama et al.'s SEQ ID NO:12 21-mer could somehow be read as being "perfectly complementary" to the present application's SEQ ID NO:1 17-mer, the rejection would still fail for at least the reason that there would have been no motivation to produce a single-stranded RNA with the same sequence as Sugiyama et al.'s 21-mer DNA. The Office action at pages 4-5 does address motivation, proposing two alternative motivations to make such an RNA:

(a) *"to use the RNA-based antisense nucleic acid to detect the RNA level of WT1 in cancer cell sample,"* and

(b) *to "inhibit the WT1 expression level at the RNA level."*

Applicants submit that one of ordinary skill in the art would not have considered either of these proposed "motivations" to constitute an actual reason to make the presently claimed composition.

Regarding the proposed motivation in (a) above, Applicants are unsure whether the Office is suggesting that an RNA version of Sugiyama et al.'s 21-mer can be utilized as a primer in RT-PCR or instead suggests that the RNA could be used as a probe for Northern blots, as both RT-PCR and Northern blots are generally used to detect levels of RNA in samples. Applicants are unaware that RNA-based primers are ever used in RT-PCR, and ask the Examiner to point to

evidence supporting such a motivation, if that is indeed what was meant. The only PCR primers taught by Sugiyama et al. were, of course, DNA-based primers (see Tables 1-3 of Sugiyama et al.). Single-stranded DNAs tend to be far more stable, and thus easier to store and use, than single-stranded RNAs, due to the general problem of contamination of samples, reagents, and equipment with ubiquitous RNAses. If instead the Examiner meant "detect the RNA level" to imply use of a Northern blot, Applicants submit that hybridization probes used in Northern blot assays are usually DNA, not RNA, and are typically much longer than the 17-mer of claim 24 or the 21-mer DNA of Sugiyama et al. See, e.g., the article by Trayhurn about Northern blots in Proc. Nutr. Soc. 55:583-589 (1996) (document 4 in the Information Disclosure Statement filed on even date herewith), which says that the single-stranded probe is customarily a cDNA, but can instead be an oligonucleotide 30 to 40 bases in length. The Examiner is respectfully asked to indicate where in the art can be found an expectation that an RNA version of Sugiyama et al.'s 21-mer could be successfully used either as a RT-PCR primer or as a probe in a Northern blot. Further, the Examiner is asked to make explicit why one of ordinary skill would have had a rational reason to make the 21-mer RNA for either of those purposes, where DNA is known to be much stabler than RNA, and where longer probes are generally considered necessary for Northern blots. Applicants submit that it would not have been obvious to prepare a single-stranded RNA version of Sugiyama et al.'s SEQ ID NO:12 DNA primer for use as proposed in (a) above.

The "motivation" postulated in (b) above appears to be based on an assumption that the art would have expected an RNA having the sequence of Sugiyama's SEQ ID NO:12 to be able to inhibit WT1 expression. The Office cites no evidence or reasoning to support this assumption, and Applicants can find nothing to support it in Sugiyama et al. or any other art cited in this rejection. In fact, those of skill in the art realized that not all antisense RNAs possess such an activity. See, for example, Davies et al., Human Molecular Genetics 13:235-246, 2004 (document A9 in the Information Disclosure Statement filed January 22, 2008), which says in the carryover sentence of pages 236-237, "**It has been documented that, while siRNA is generally**

highly effective in repressing gene expression in mammalian cells, the effectiveness of any particular siRNA is difficult to predict." (Emphasis added.) See also McManus et al., J. Immunol. 169:5754-5760, 2002 (document 5 in the Information Disclosure Statement filed on even date herewith), which says at page 5757, left column, that "**we observed that the majority of the synthetic CD4 and CD8α siRNAs were noneffective at silencing.**" Figure 3B of McManus et al. shows that only one of four siRNAs targeting CD8 mRNA and only one of five siRNAs targeting CD4 mRNA were found to be capable of inhibiting expression of the respective mRNA. Given the unpredictability of this field, Applicant submits that those of skill in the art would not have had a reasonable expectation that an RNA version of Sugiyama et al.'s SEQ ID NO:12 would be able to inhibit expression of Wt1 mRNA.

Third, the Office has not suggested any reason that one of skill in the art would have selected Sugiyama et al.'s SEQ ID NO:12, out of the six antisense DNA primers disclosed in Sugiyama et al., as the particular one to produce in RNA form (and then shorten it from 21 nucleotides to the exact 17 nucleotides required by claim 24). Selection of this particular primer as the one to modify is clearly based solely on hindsight, and not on any teaching in the art nor any rational justification that Applicants can discern.

In the "Response to Arguments" section of the Office action beginning at page 5, the Office says that "there are only two types of naturally occurring nucleotides: DNA and RNA" and that antisense RNA can bind to complementary RNA. According to the Office action,

> one of ordinary skill in the art in need of an antisense oligonucleotides sequence of SEQ ID NO:12 that binds and hybridizes an RNA sequence (e.g., mRNA) for directly targeting the complementary mRNA sequence would have been sufficiently motivated to make an RNA compound comprising SEQ ID NO:12 of Sugiyama et al. There is nothing challenging or difficult or unpredictable about synthesizing an RNA molecule having the already known nucleotide sequence disclosed in the art.

It appears from the above that the Office is of the view that the mere fact that RNAs can hybridize to complementary RNAs is sufficient to motivate one of skill in the art who was "in need of an antisense oligonucleotide" that would hybridize to a particular RNA sequence to

produce an antisense RNA, rather than an antisense DNA. Applicants disagree. Whether one of skill in the art would select RNA or DNA as the antisense nucleic acid depends on the purpose. As pointed out above, DNA is perfectly capable of hybridizing to complementary RNA, and is far more stable than RNA, so is generally used for both primer and probe purposes. RNA is the nucleotide of choice for siRNA purposes, but as explained above, there would have been no reason to expect that an RNA version of Sugiyama et al.'s SEQ ID NO:12 would have any activity as an siRNA. Further, even if one did produce an RNA version of Sugiyama's SEQ ID NO:12, it would be a 21-mer and so not "perfectly complementary" with the 17-mer that is the present application's SEQ ID NO:1, as required by claim 24. The Office has suggested no reason that one of ordinary skill would produce an arbitrarily shortened RNA version of Sugiyama et al.'s 21-mer.

In view of the above, Applicants submit that a *prima facie* case of obviousness has not been made, and ask that the rejection over Sugiyama et al. in view of Ast et al., Mallardo et al., Jin et al., and Vickers et al. be withdrawn.

2. Claim 24 was also rejected as obvious over Ware et al. (US 6,232,073 B1) in view of Ast et al. (Nucleic Acids Res., 1997, 25:3508-3513); Mallardo et al. (Mol. Biol. Cell, 2001, 12:3875-3891); Jin et al. (Cancer Res, 2003, 63:6154-6157); and Vickers et al. (J. Biol. Chem., 2003, 278:7108-7118). The Final Office action at pages 6-7 points to Ware et al.'s disclosure of what Ware et al. labels "SEQ ID NO:30." Ware et al.'s SEQ ID NO:30 is a 21-mer DNA identical to SEQ ID NO:12 of Sugiyama et al., discussed above. Ware et al. utilized this 21-mer DNA as a RT-PCR primer (see item 13 in Table 1). As was the case for the rejection over Sugiyama et al. discussed above, the Office action acknowledges that "Ware et al. do not teach a single-stranded RNA or double-stranded RNA comprising RNA of SEQ ID NO:30."

The rejection based on Ware et al. combined with Ast et al., Mallardo et al., Jin et al., and Vickers et al. is essentially the same as the rejection based on Sugiyama et al. combined with the same four secondary references. Applicants submit that, for the same reasons as outlined above, the rejection over Ware et al. combined with Ast et al., Mallardo et al., Jin et al., and Vickers et al. is not warranted and should be withdrawn.

The fee in the amount of $1,110.00 for the Petition for Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-0169US1.

Respectfully submitted,

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